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PATENT
Docket No. 0933-0154P

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS: Veli-Matti LEHTOLA et al. CONF.: 7050

APPLN. NO.: 09/486,971 GROUP: 1615

FILED: May 19, 2000 EXAMINER: R. Bennett

RB 4/9/02

FOR: PHARMACEUTICAL PREPARATION COMPRISING CLODRONATE AS ACTIVE INGREDIENT AND SILICIFIED MICROCRYSTALLINE CELLULOSE AS EXCIPIENT

DECLARATION UNDER 37 C.F.R. § 1.132

Assistant Commissioner of Patents
Washington, DC 20231

Sir:

I, Dr. Juhani Posti, do declare and say as follows:

1. I am a graduate of Pharmacy of the University of Helsinki, in 1970, and I have subsequently attained the Dr.sc.nat. degree in Pharmacy at the Swiss Federal Institute of Technology (ETH Zürich), in 1978.

2. I have been employed by Leiras R&D since January 1978 in the following positions:

January 1978 - April 1983: Research Manager; May 1983 - March 1984: Pharmaceutical Development Manager; April 1984 - December 1985: Research Director; January 1986 - August 1988: Director, Pharmaceutical R&D; September 1988 - December 1991: Assistant Director, Pharmaceutical R&D; January 1992 – December 2000: Assistant Director, Regulatory Services.

My current position since January 2001 is Associate Director, Pharmaceutical Adviser of CMC Development of Leiras.

3. The following comparative tests were performed under my direction and control:

Manufactured trial batches

The tests included four trial batches of which two were manufactured according to the composition described in the patent application (Example 7). The other two batches were made essentially according to the formula (Example 1) described in the patent by Posti et al., with slight modifications in order to attain the desired mean weight of 1177 mg for the tablets.

Batches made according to the formula in the current Patent application, Example 7 (Batches 1 and 2)

Compositions per one tablet of the batches:

	Batch 1	Batch 2
Disodium clodronate tetrahydrate (responding anhydrous disodium clodronate)	1000 mg (800 mg)	1000 mg (800 mg)
Silicified microcrystalline cellulose (SMCC)	165 mg	-
Microcrystalline cellulose (MCC)	-	161.7 mg
Colloidal anhydrous silicon dioxide (SiO_2)	-	3.3 mg
Croscarmellose sodium	22 mg	22 mg
Stearic acid	15 mg	15 mg
Magnesium stearate	8 mg	8 mg
Ethanol (evaporating solvent for stearic acid)	q.s.	q.s.

The only difference between the manufacturing of these two batches was that batch 1 contained SMCC as tablet binder whereas batch 2 contained plain MCC, and the amount of silicon dioxide equal to the silicon dioxide content of the SMCC (SMCC is composed of 98% of MCC and of 2% of SiO_2) was added to the mass during the process.

The process consisted of roller compaction of the active ingredient, followed by lubrication with stearic acid in ethanol solution. The moistened drug granules were dried and sieved, and all excipients other than magnesium stearate were added under mixing. Magnesium stearate was admixed just prior to tabletting, and the final mix was compressed under constant pressure into tablets with mean weight of 1189 mg. Tablets of both batches attained the same mean weight.

Test results of the batches 1 and 2

	Batch 1 with SMCC	Batch 2 with MCC + SiO_2
Crushing strength / N	Mean: 155 N	Mean: 145 N
	Range: 147 – 163 N	Range: 136 – 157 N
Friability / %	0.37 %	4.8 %

Crushing strength of the tablets with SMCC (batch 1) was slightly higher, but the values for both batches represented, however, reasonable hardness levels considering handling of the tablets.

Even though the tablet hardness can be considered proper for both batches, there is a significant difference in friability (= resistance to attritional wear) of the tablets between the two batches. The friability of the SMCC batch is low and the result fulfils the pharmacopoeial requirement of less than 1 % friability, while the friability of the tablets with MCC + SiO_2 is not acceptable considering industrial manufacturing of tablets.

Batches made according to the patent by Posti et al. (Batches 3 and 4)

These two batches were also manufactured using clodronate pre-densificated by the roller compactor.

Compositions per one tablet of the batches:

	Batch 3	Batch 4
Disodium clodronate tetrahydrate (responding anhydrous disodium clodronate)	1000 mg (800 mg)	1000 mg (800 mg)
Povidone	17.70 mg	17.70 mg
Croscarmellose sodium	17.35 mg	17.35 mg
Silicified microcrystalline cellulose (SMCC)	23.29 mg	-
Microcrystalline cellulose (MCC)	-	22.83 mg
Lactose monohydrate	70.75 mg	70.75 mg
Stearic acid	11.06 mg	11.06 mg
Colloidal anhydrous silicon dioxide (SiO_2)	11.35 mg	11.80 mg
Talc	20.06 mg	20.06 mg
Magnesium stearate	5.45 mg	5.45 mg
Ethanol (evaporating solvent for stearic acid and povidone)	q.s.	q.s.
Purified water (evaporating solvent for povidone)	q.s.	q.s.

The amount of added SiO_2 in the SMCC batch (batch 3) was slightly lower in order to balance the actual total amounts of SiO_2 between the two batches. This was achieved by also taking into account the amount of SiO_2 included in 23.29 mg of SMCC (2 % of SiO_2 is included in the SMCC, corresponding to 0.46 mg of SiO_2 per one tablet).

In the first stage, the drug substance clodronate was wetted with ethanol/water solution of povidone, followed by sieving and drying. Then SMCC (batch 3) or MCC + 0.46 mg/tablet of SiO_2 (batch 4) and croscarmellose were admixed to the drug granulate. The mass was lubricated with ethanolic solution of stearic acid and dried. To the dried mass, talc, lactose and SiO_2 (11.35 mg /tablet for both batches 3 and 4) were added by mixing, followed by addition of the lubricant magnesium stearate. Finally, the batches were tabletted under constant pressure into tablets of the desired weight.

Test results of the batches 3 and 4

Mean weight of the tablets:
SMCC batch 3:1196 mg; MCC + SiO2 batch 4: 1154 mg
(Requirement for the mean weight 1177 mg ± 2,5 % = 1147,6 mg – 1206,4 mg).

	Batch 3 with SMCC	Batch 4 with MCC + SiO_2
Crushing strength / N	Mean: 161 N	Mean: 137 N
	Range: 139 – 191 N	Range: 124 – 155 N
Friability / %	0.24 %	22.8 %

The crushing strength of the tablets with SMCC (batch 3) was clearly higher than of the tablets with MCC + SiO_2 (batch 4). Though, it should be noticed that also the crushing strength of the MCC + SiO_2 batch represents a reasonable level.

Even though the tablet hardness for both batches can be considered acceptable and equivalent in practice, there is a marked difference in friability of the tablets between the two batches. The friability of the SMCC batch is low, the result fulfilling the same pharmacopoeial requirement as the trial batch 1, while the friability of the tablets of the MCC + SiO_2 batch is far from the acceptable level considering industrial manufacturing and required quality of tablets in general.

4. The significance of the results of these comparative tests is as follows.

It can be concluded that the above results clearly demonstrate the advantageous properties of SMCC regarding compressibility of the powder mass, and friability of the resulting tablets containing disodium clodronate as the active ingredient. The ability of SMCC to form strong compacts is particularly important under circumstances like this, where the amount of the active ingredient is very high compared to the practically feasible amounts of binders and other excipients in the formulation that can be used to attain a tablet of reasonable size and weight.

Although the crushing strength of the tablets with MCC +SiO_2 is generally satisfactory, the tablets fail to maintain their integrity in the pharmacopoeial friability test. The difference between tablets obtained using SMCC or MCC + SiO_2, on the other hand, as a tablet binder is very clear.

To conclude, disodium clodronate tablets prepared with SMCC as an excipient show the required hardness and friability properties necessary for proper transportability or further processability (e.g. coating) of the tablets. Disodium clodronate tablets obtained using instead of SMCC the separately, but in corresponding quantitative amounts added excipients MCC + SiO_2 are very unsatisfactory with respect to friability of the tablets.

I hereby declare that all statements made herein of my own knowledge are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 21 February 2002

By Juhani Posti

Dr. Juhani Posti
Associate Director
Pharmaceutical Advisor
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